Random number generation deficits in patients with multiple sclerosis: Characteristics and neural correlates

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Abstract

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Keywords

Random number generation; mental dice task; multiple sclerosis, neural correlates

Abbreviations

FOD = First-order differences; MDT = Mental dice task; MS = Multiple Sclerosis; RNG = Random number generation; ROI = Region of interest; RRMS = Relapsing-remitting Multiple Sclerosis; TPI = Turning point index; WM = White matter

1. Introduction

As smart human brains are in spotting patterns and following rules, as miserably they fail in attempting to be unpredictable. A case in point is our inability to generate random sequences of responses. Instructions of a random number generation (RNG) task require subjects to arrange numbers in a sequence "as random as possible", implicitly asking to avoid any algorithm and to disobey any rule. Under a huge range of conditions (Brugger, 1997) healthy volunteers were found unable to follow these instructions, and so were patients with various neuropsychiatric diseases (Brown, Soliveri, & Jahanshahi, 1998; Brugger, Monsch, Salmon, & Butters, 1996; Ho, Sahakian, Robbins, & Barker, 2004; Salamé & Danion, 2007; Spatt & Goldenberg, 1993). A limited capacity of working memory and executive functions have been implied in the failure to produce unpredictable, or random sequences of response alternatives (Baddeley, 1966, 1998; Joppich et al., 2004; Maes, Eling, Reelick, & Kessels, 2011; Miyake et al., 2000). Neuroimaging studies have largely supported the assumed implication of the (pre)frontal lobes for RNG (Artiges et al., 2000; Itagaki, Niwa, Itoh, & Momose, 1995) and non-invasive intervention methods have suggested their causal involvement (Jahanshahi et al., 1998; Knoch, Brugger, & Regard, 2005).

Facing the large and rapidly growing number of behavioral and functional neuroimaging studies on RNG, one is left wondering why the neuroanatomical correlates of RNG have never been examined in a structural imaging approach. The present study was aimed at filling this gap in patients with multiple sclerosis (MS), a disease whose impact on RNG has, to the best of our knowledge, never been studied. MS, the most common autoimmune disorder affecting the central nervous system, is historically considered a white matter (WM) disease, with focal demyelinating lesions in the WM being the pathological hallmark. However, several recent neuropathological studies disclosed a relevant involvement of gray matter areas including the cerebral cortex (Calabrese et al., 2015; Geisseler et al., 2016). Brain integrity, captured by various imaging techniques, has been shown to correlate with cognitive

impairment (for review see Rocca et al., 2015), which is recognized as an important feature of MS, prevalent in 43-70% of MS patients (Chiaravalloti & DeLuca, 2008; Pflugshaupt, Geisseler, Nyffeler, & Linnebank, 2016). Although processing speed (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Roth, Denney, & Lynch, 2015) and episodic memory (e.g. Rogers & Panegyres, 2007) seem to be the most prominent cognitive feature of MS, these patients often exhibit significant deficits in executive functions (Geisseler et al., 2016; Henry & Beatty, 2006). Against this background, it appears tempting to assume that MS patients exhibit impaired performance in generating random sequences of numbers.

The aim of the present study is two-fold. On the one hand, we planned to examine the impact of MS on randomization performance; on the other hand, we wanted to explore, for the first time, structural brain correlates of RNG. Specifically, we predicted an impaired randomization performance by the patients with MS relative to a carefully matched healthy control group. As a first step in uncovering the neuroanatomical correlates of RNG, we planned to analyze associations between brain structure and RNG performance in healthy participants and, in the patient group, between cortical and subcortical damage and RNG performance.

2. Material and methods

2.1 Participants

Forty-four patients with a definite diagnosis of relapsing-remitting multiple sclerosis (RRMS) according to the 2010 McDonald criteria (Polman et al., 2011) and 39 age-, gender-, handedness- and education-matched healthy controls participated in this study. Inclusion criteria for the patient group were no relapse or steroid-treatment during the last two months, no current or past neurological disorder in addition to multiple sclerosis, and no psychiatric disorders apart from MS-related depressive mood state. The local ethics committee approved

the study, and all subjects gave written informed consent before participation. Control participants received financial compensation.

2.2 RNG task, performance measures and hypotheses

The Mental Dice Task (MDT) was administered in its standardized form (Brugger et al., 1996). Subjects were instructed to imagine repeatedly throwing a die and to orally report the number that would show up, i.e., they had to generate numbers from 1 to 6 in a random fashion. Subjects were instructed to synchronize their response with a pacing auditory stimulus, which was a beeping sound presented at 1 Hz. A total of 66 valid responses were recorded.

While there are many different measures of (non)randomness, we focused on three variables, which were calculated by means of a freely available computer program (http://www.lancs.uk/staff/towse/rgcpage.html). First, we determined the distribution of first-order differences (FODs), reflecting the arithmetic difference between each response and the preceding one. Thus, FODs may vary between -5 (6 followed by 1) and +5 (1 followed by 6). The elegance of FODs is that their graphical depiction clearly illustrates the frequencies of all named combinations of the digits to be randomized in one curve (see Figure 1). For the present purpose, it thus displays those pairs of consecutive numbers for which group differences were predicted alongside those for which no such differences were predicted. Specifically, FOD values of +1 reflect a counting strategy, which we predicted to be pronounced in patients with MS, under the assumption of an impaired executive control of automatized responding (i.e., counting). Some authors have reported an excess of counting in steps of 2 (FOD = +2), in addition to counting in the narrow sense (i.e. in steps of 1; Jahanshahi et al., 1998) and the display would allow us to check for the frequency of +2 pairings as well. FOD values of 0 represent the number of direct repetitions of any of the 6 digits to be randomized. We predicted a comparable degrees of repetition avoidance for both

groups, as repetition (alternation) behavior may be under hippocampal, rather than prefrontal control (Lalonde, 2002). A second measure, the turning point index (TPI) captures the frequency of shifts between ascending and descending sequences. TPI is reported as a percentage score, meaning that values greater than 100 indicate too many turning points - relative to a theoretical distribution of random responses - whereas values less than 100 indicate fewer turning points than expected. We predicted that patients would show a lower TPI than control participants because of more pronounced perseverative tendencies leading to longer ascending and descending sequences. Finally, as a global measure of randomness, Evans' random number generation index (Evans, 1978; RNG index) was calculated. As a general redundancy measure, this index is among the most frequently used measures of non-randomness in the literature on RNG. It varies between 0 to 1, with higher indices representing less randomness, which was predicted for the patient group on grounds of their hypothetically enhanced response stereotypy. Further information and mathematical details of these calculations are described elsewhere (Towse & Neil, 1998). Conceptually, both our counting measure (FOD=1) and the TPI primarily rely on frontal executive functions; we did not use a measure tapping more into the working memory components of RNG.
Additionally, and besides these measures of sequential non-randomness, two non-sequential variables of the MDT were considered, i.e., the number of rule breaks (i.e., producing out-of-category digits such as 7) and the total number of skipped beats of the metronome. Both rule breaks and a measures of time stress have proved useful in monitoring executive function demands in RNG (e.g. Gottselig et al., 2006).

2.3 MRI data acquisition, post-processing and hypotheses

The MRI scan was performed within one month of the neuropsychological examination. All images were acquired using a 1.5-T scanner (Siemens Magnetom Avanto^{TM}) equipped with a SQ-engine gradient (45m/T/m @ 200 T/m/s) using a dedicated 32-channel head coil. No

hardware upgrades of the scanner occurred during the study period. The following sequences were obtained from all subjects: (1) Double Inversion Recovery sequence (DIR) (voxel size =1.5 x 1.5 x 1.5 mm, slice thickness = 1.5 mm, repetition time = 7500ms, echo time = 308ms); (2) T1-weighted MPRAGE (voxel size = 1 x 1 x 1 mm, slice thickness = 1 mm, repetition time = 2420 ms, echo time = 4.18 ms) and (3) a T2-weighted FLAIR (voxel size = 0.9 x 0.9 x 2.0 mm, slice thickness = 2 mm, repetition time = 5000 ms, echo time = 342 ms). Cortical lesions were defined according to the consensus recommendations of Geurts and colleagues (Geurts et al., 2011). Consequently, cortical lesions are those lesions appearing hyperintense on DIR images compared to surrounding normal-appearing grey matter, entirely or partly located in the cortical grey matter and occupying at least three voxels. DIR-hyperintense lesions were identified and manually delineated with MRIcron (http://sph.sc.edu/comd/rorden/mricron), which was further used to measure total lesion volume. The same procedure was applied to FLAIR images to identify and segment T2-hyperintense lesions. An experienced rater assessed all images, supervised by a neuroradiologist. A non-parametric mapping software (Rorden, Karnath, & Bonilha, 2007) was used to analyze possible associations of behavioral performance with the spatial distribution of lesions, i.e. voxel-based lesion symptom mapping (VLSM). Central brain atrophy was examined by measuring the width of the third ventricle, implemented according to the procedure defined by Benedict and colleagues (Benedict et al., 2006). Similar to many other studies on cognition in MS (e.g. Benedict et al., 2006), we expect a wider third ventricle to be associated with poorer behavioral performance. Cortical thickness evaluation was performed by means of Freesurfer image analysis suite, which is documented and freely available online (http://surfer.nmr.mgh.harvard.edu). Further information and technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). To detect possible misclassifications of white and grey matter due to multiple sclerosis lesions, all images were visually inspected after the segmentation of grey

and white matter. In one patient, a semi-automated correction of topological defects was required by manually adding control points. Global cortical thickness as well as cortical thickness estimates for the regions resulting from automated parcellations (Desikan et al., 2006) were extracted from the Freesurfer software for further analyses. In line with the hypothesis that RNG performance rely on frontal functions, we mainly focused on frontal regions of interest (ROI), whereas temporal and parieto-occipital ROI were used as control regions.

2.4 Statistical analyses

Statistical analyses of the demographical and cognitive data, including group comparisons, were performed with SPSS (IBM, Chicago, USA, Version, 21.0, http://spss.com). Unless otherwise stated, a p-level below 5% was considered statistically significant. Assumptions for normality were tested for all continuous data with Kolmogorov-Smirnov tests. In case of normally distributed variables, group comparisons and correlational analyses were based on parametric tests (independent t-tests, Pearson correlation). When variables were not normally distributed, non-parametric tests (Mann-Whitney U test, Spearman correlation) were applied. Concerning all group comparisons, correlational analyses and ROI analyses, Bonferroni correction was used to prevent alpha error inflation. For the VLSM we performed Brunner-Munzel tests (Brunner & Munzel, 2000) at a threshold of 5% FDR to identify lesioned voxels associated with RNG performance. Only voxels affected in at least two patients were considered for analysis.

3. Results

3.1 RNG findings

Demographic characteristics and MDT test results are reported in Table 1. The distribution of FODs is shown in Figure 1, and an overview of the RNG parameters is given in Table 1.

Patients displayed significantly (T(67.9) = 3.010; p = 0.004) more forward counting steps (Mean = 15.91; SD = 8.335) than healthy controls (Mean = 11.54; SD = 4.541). Furthermore, the latter showed more backward counting steps of two than the patients (FOD = -2; T(81) = -2.490; p = 0.015). No differences between groups were observed in the number of repetitions (FOD = 0). Patients (Mean = 77.02; SD = 18.17) had a smaller TPI than controls (Mean = 89.8, SD = 13.33), i.e. they showed less changes from ascending to descending sequences and vice versa (T(81) = -3.624, p < 0.001). RNG indices did not differ significantly between groups (Z = -1.437; p = 0.151). Regarding non-sequential measures, MS patients showed a higher susceptibility to rule breaks (Z = -2.431; p = 0.014) as well as to skip beats of the metronome (Z = -4.983, p < 0.001) than the control group.

Correlational analyses within the patient group yielded no relationship between RNG parameters and age, education, disease severity (EDSS), fatigue or depressive mood (all p > 0.050).

3.2 MRI findings

Relative to controls, patients showed significant cortical thinning and widening of the third ventricle (both $p < 0.010$). Results of the univariate correlation analyses between the global atrophy and the RNG parameters as well as between the lesion and the RNG parameters within the patient group are summarized in Table 2.

Within the patient group, mean global cortical thickness showed a significant negative correlation with skipped beats in the MDT ($r_s = -0.411$, $p = 0.006$), i.e. a thinner cortex was associated with more skipped beats. In contrast, global cortical thickness was not associated with TPI, counting tendency, or the number of rule breaks (all $p > 0.050$). The width of the third ventricle did not correlated with any of the RNG parameters. Regarding lesion parameters, DIR-hyperintense lesion volume correlated with the counting tendency (r = 0.402; $p < 0.007$; Figure 2). However, both DIR-hyperintense cortex-involving (r = 0.306; p =

0.045) as well as FLAIR-hyperintense lesion volumes (r = 0.345; p = 0.022) were uncorrelated with the TPI and the non-sequential parameters. None of the global MRI variables correlated with TPI or the number of rule breaks.

On a regional level, ROI analyses revealed no significant correlation between counting tendency and the cortical thickness in frontal regions of interest when applying strict Bonferroni correction. Supplementary Table 1 displays r-values and uncorrected p-values (which ranged between r = -0.359, $p < 0.009$ and r = 0.018, $p < 0.454$) showing an association between counting tendency (measured by FOD 1) and cortical thickness in the left pars orbitalis as well as with bilateral cortical thickness in the pars triangularis of the inferior frontal gyrus. No significant correlation was observed between the temporal and parietal control ROIs with any sequential parameters. Regarding non-sequential parameters, the ROI-based correlational analyses did also not survive Bonferroni correction; Supplementary Table 2 displays uncorrected p-values showing associations with cortical thickness in several regions of interests in frontal, temporal and parieto-occipital areas. Concerning the topological relation of lesions (cortical and T2-hyperintense lesion) with RNG parameters, VLSM revealed no significant clusters.

Within the control group, the only significant correlation between global cortical thickness and the RNG parameters was that with skipped beats (r_s = -0.342, $p < 0.033$). No significant correlations were observed between the width of the third ventricle or global cortical thickness and any of the RNG parameters, and the regional ROI analyses were also uncorrelated with both sequential and non-sequential measures of the MDT (see Supplementary Table 3 for uncorrected correlation values, again showing associations of nonsequential parameters with several widespread areas).

4. Discussion

The current study examined the behavioral performance and neuroanatomical underpinnings of RNG in a cohort of MS patients, compared with a group of matched healthy controls. As predicted, random number sequences generated by MS patients were more stereotyped than those of healthy controls. More precisely, MS patients showed more ascending counting behavior than control subjects. This corresponds well with previous reports of a deterioration of randomization performance in the presence of a neurological disorder (Brown et al., 1998; Brugger et al., 1996; Ho et al., 2004) and with the observation of executive dysfunction in MS (Drew, Tippett, Starkey, & Isler, 2008; Geisseler et al., 2016). Patients did not differ from controls in the global measure of randomness (RNG index; 0.47 and 0.43, respectively), perhaps due to a "floor effect"; both groups scored far from the value obtained in 100 simulations of 66 dice throws, i.e. 0.36; see (Brugger et al., 1996). Relative to healthy controls, patients also exhibited problems in non-sequential parameters. They showed pronounce difficulties in keeping pace (1Hz) and in avoiding invalid numbers (e.g. 7). The former problem is consistent with reports that the primary cognitive deficit in MS patients may be generalized slowing of information processing speed (DeLuca et al., 2004). Using sleep deprivation, Gottselig et al., (2006) induced such slowing in healthy research participants, who had to generate random numbers. However, an excess of skipped beats may also reflect enhanced task difficulty. Consequently, the non-sequential variable of skipped beats in RNG may be a useful parameter for a brief and valid assessment of information processing speed and/or experienced task difficulty.

Cognitive impairment in MS patients has been related to a number of structural abnormalities in the past. Demyelinated T2 lesions in the white matter – the pathological hallmark of MS – are only modestly correlated with cognitive impairment (Lazeron et al., 2005; Rao, Leo, Haughton, St Aubin-Faubert, & Bernardin, 1989). Higher correlations are observed between cognitive performance and third ventricle width, which is traditionally considered the best single MRI predictor for MS-related cognitive impairment (Benedict et al., 2004, 2006). More

recent research highlights cortical pathology as one of the major substrates of cognitive decline in MS (for a review see Messina & Patti, 2014). Our clinico-anatomical correlation analyses revealed two main findings that survived Bonferroni correction: First, increased counting in MS patients was associated with higher cortical lesion load. Second, increased number of skipped beats were related to widespread cortical thinning. Moreover, uncorrected findings showed an association between counting tendency and the cortical thickness in the left pars orbitalis and bilateral in the pars triangularis of the inferior frontal gyrus. These findings are unexpected on the basis of previous functional imaging or TMS studies showing an association between counting bias and primarily the dorsolateral prefrontal cortex (DLPFC) (Jahanshahi et al., 1998; Knoch et al., 2005). No structural correlates could be found for the number of rule breaks and the TPI-measure of sequential randomness. FLAIR-hyperintense lesion load did not correlate significantly with any of the behavioral parameters. The association between a widespread thinner cortex and an increased number of skipped beats is in line with previous studies emphasizing the relationship between volume/thickness of the neocortex and mental processing efficiency in MS (Amato et al., 2007; Benedict et al., 2006). We propose that the number of skipped beats reflect speed and attention (and arguably experienced task difficulty), both in MS patients and healthy controls.

To the best of our knowledge, this is the first study evaluating the RNG performance by means of structural MRI. Our results suggest an association between cortical pathology and RNG performance. On a behavioral level, it can be concluded that even when compensating for difficulties by slowing the rate at which they produced numbers, MS patients commit rule breaks and cannot sufficiently suppress a counting algorithm. RNG may be a useful tool in the clinical monitoring of MS. As the task is highly resistant to practice effects (Brugger, 1997; Jahanshahi, Saleem, Ho, Dirnberger, & Fuller, 2006), it may prove particularly suitable for monitoring cognitive capacity over time.

Future studies could employ lesion-symptom mapping analyses in patients with focal lesions to establish connections between brain circuitry and selected measures of sequential non-randomness. Structural connectivity analyses will also be needed to better understand neurostructural underpinnings of randomization performance in health and disease.

Conflict of interest

ML received grants, funding or honoraria from Bayer, Biogen, Genzyme, Merck, Novartis and Teva. The other authors report no disclosures.

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Table 1: Demographic characteristics and measures of performance on the MDT of MS patients and healthy controls

	MS patients	Controls	*p*-value
Number	44	39	-
Gender [m/f]	10/34	6/33	0.397
Age [years], mean (SD)	39.02 (9.4)	38.53	0.813
Education [years], mean (SD)	14.6 (3.1)	14.3(2.4)	0.690
EDSS, mean	2.6	-	-
Disease duration [months], mean	79.5	-	-
RNG, mean	0.47	0.43	0.151
Counting [FOD 1], mean	15.91	11.54	0.004**
Repetitions [FOD 0], mean	3.11	3.51	0.699
TPI, mean	77.02	89.84	< 0.001***
Skipped beats, mean	6.52	0.18	< 0.001***
Rule breaks, mean	0.37	0.10	0.014*

Abbreviations: EDSS = Expended disability status scale, RNG = Random number generation, FOD = First order difference, TPI = Turning point index

Table 2: Spearman correlations between measures of the Mental Dice Task (MDT) and neuroimaging parameters in patients with relapsing-remitting multiple sclerosis (n=44)

	Sequential measures		Non-sequential measures	
	TPI	Counting tendency	Skipped beats	Rule breaks
	r_s (*p-value*)	r_s (*p-value*)	r_s (*p-value*)	r_s (*p-value*)
Atrophy parameters				
Cortical thickness	0.078 (*0.614*)	-0.161 (*0.296*)	-0.411(*0.006*** [a])	0.112 (*0.467*)
Third ventricle width	-0.110 (*0.477*)	0.332 (*0.028*)	0.237 (*0.122*)	0.174 (*0.259*)
Lesion parameters				
T2-hyperintense lesion load	-0.190 (*0.217*)	0.270 (*0.076*)	0.345 (*0.022*)	0.015 (*0.922*)
Cortical lesion load	-0.053 (*0.731*)	0.402 (*0.007*** [a])	0.306 (*0.043*)	-0.094 (*0.545*)

Abbreviations: TPI = Turning point index
[a] The correlation remained significant when using a stringent Bonferroni correction (alpha = 0.05/8 = 0.00625)
* $p < 0.05$; ** $p < 0.01$

Figures

Figure 1: Distribution of first-order differences (FODs).

Caption:
Avoidance of repetitions is demonstrated at point 0 on the x-axis, forward counting at point 1, backward counting at point -1.

Figure 2: Correlation between cortical lesion volume (cm^3) and the counting tendency (frequency of FOD 1).

Caption:
Only patients with a minimum of one cortical lesion are included.

Supplementary material caption:

Supplementary Table 1: r- and uncorrected p-values of the sequential parameters within the patient group

Supplementary Table 2: r- and uncorrected p-values of the non-sequential parameters within the patient group

Supplementary Table 3: r- and uncorrected p-values of the RNG parameters within the control group

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